A Comparison of oral Clonidine versus oral Diazepam premedication for maintaining haemodynamic stability during craniotomy

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Abstract

Background: Clonidine is an alpha-2 adrenergic agonist, which is a centrally acting antihypertensive drug. The recent reviews had shown that clonidine has sedative, anxiolytic, analgesic, and anesthetic-sparing properties which would stabilises the circulatory system and maintains the perioperative stress response at a lower level.

Aim: To compare the efficacy between oral clonidine and oral diazepam as a premedication in maintaining the hemodynamic stability during craniotomy surgeries.

Materials and Methods: Fifty patients with various types of intracranial tumours who were planned for elective surgical excision were included for the study. Group 1 patients (n=25) received 0.2mg/kg of diazepam and the Group 2 patients received 3.5mcg/kg body weight of clonidine orally 90mts before induction. Recordings of systolic, diastolic, mean blood pressure and heart rate was done from the arterial tracing, the transducer kept at the level of the external auditory meatus. It was made every 10mts for the first 2hours from the time of dural opening.

Results: Of all the various hemodynamic parameters the heart rate alone had shown a statistically significant reduction over the period of 2 hours in patients among the clonidine group. The blood pressure parameters in both the groups had also shown reduction from base line in the first 60minutes and later on over the period of 2 hours the values had come back to that of the base line values and no statistically significant difference had occurred between the two groups and also the antisialagogue activity is more with clonidine than diazepam.

Conclusion: The hemodynamic response during craniotomy was better controlled with clonidine which has shown a better response in controlling tachycardia and maintaining the systolic, diastolic and mean arterial pressures than diazepam. So clonidine can be considered as a good drug for premedication in craniotomy surgeries in comparison with diazepam.

Keywords: Clonidine, Diazepam, Hemodynamic parameters.

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Introduction

The major goal of neuroanaesthesia is to maintain good operating conditions by ensuring stable cerebral haemodynamics without causing sudden increase in intracranial pressure or acute brain swelling. Furthermore, fast recovery from anaesthesia is often preferred to allow immediate neurological evaluation. During recovery increase in arterial blood pressure and heart rate usually pose a risk of developing postoperative haematoma[1].

Opioid analgesics have the ability of preventing increase in blood pressure and heart rate during the period of awakening and extubation but it pose a risk of developing respiratory depression such that the carbon dioxide tension increases which would invariably cause an increase in the intracranial pressure[2].

Due to the fragility of the neurological structures maintaining a bloodless field in order to stable the hemodynamic response is of utmost important for brain surgeries[3]. Decreased bleeding reduces the need for blood transfusion so the risk of post-transfusion complications is also reduced.

Controlled hypotension has been used with success in orthopedic surgery and the same has been applied for both spine and brain surgeries[4-7]. Agents that are used to induce controlled hypotension include inhalation anesthetics, sodium nitroprusside, nitroglycerin, trimethaphan, alprostadil (prostaglandin E1), adenosine, remifentanil, and clonidine.

The usually preferred technique for maintaining the hemodynamic response is using a combination of remifentanil with propofol or an inhalational agent[8,9]. Alpha-2 adrenergic agonists (clonidine and dexmedetomidine) have been used successfully as adjuvants, oral premedication, and intravenous infusion during anesthesia to induce controlled hypotension[10,11].

Clonidine is an alpha-2 adrenergic agonist, which is a centrally acting antihypertensive drug. The recent reviews had shown that clonidine has sedative, anxiolytic[12], analgesic, and anesthetic-sparing (it reduces the dose of anesthetic and analgesics used intra- and postoperatively) properties which would stabilise

the circulatory system and maintains the perioperative stress response well under control[13]. In addition, clonidine also increases the cardiac baroreceptor reflex which in turn increases the systolic blood pressure, and maintains the blood pressure[14]. This characteristic is very important in neurological surgeries, as most of the brain surgeries are more prone to develop hypotension. In our country the most common drug being used as a pre-medication is diazepam and as of today very few studies had been conducted in evaluating the efficacy between diazepam and clonidine particularly in brain related surgeries and so the present study was undertaken in view of comparing the efficacy in terms of hemodynamic response between clonidine and diazepam as a pre-medication.

Aim

To compare the efficacy of oral clonidine and oral diazepam as a premedication in maintaining the hemodynamic stability during craniotomy surgeries.

Methodology

A prospective comparative study was undertaken by us on patients with intracranial tumors posted for elective excision of tumors by the neurosurgery department in our hospital during the period of Jan 2015 – December 2015. Fifty patients with various types of intracranial tumours who were planned for elective surgical excision were included for the study. Patients with brain stem lesions, cardiovascular, respiratory and renal problems, known diabetic and the hypertensive who were on anti-hypertensive drugs were excluded from the study.

After obtaining the institutional ethical clearance and the informed consent from the individual patients a detailed pre-anaesthetic examination was conducted on all the fifty patients and then they were divided into two groups of 25 each. Group 1 patients (n=25) received 0.2mg/kg of diazepam and the Group 2 patients received 3.5mcg/kg body weight of clonidine orally 90mts before induction. Random allocation of patients to each group was done by lots drawn by a person who was not taking part in the study. The premedication for the patient was ordered by that person. The drugs were given 90 minutes before the surgery with sips of water. The primary investigator of the study and the surgeon were unaware as to which group each patient belonged. The anaesthetist who was involved in the case was also unaware of the drug used.

Intravenous fentanyl 1 microgm/kg was given followed by Inj. Thiopentone 2.5% 5mg/kg and Inj. vecuronium 0.1mg/kg. Intermittent positive pressure ventilation (IPPV) was commenced with mask and circle system using 33% oxygen in nitrous oxide. Inhalational agent was not introduced until after 10mts of hyperventilation. Intravenous lignocaine 1.5mg/kg was given 90seconds before intubation. Thiopentone 1mg/kg was given 60 seconds after lignocaine and 30 seconds later intubation was done. Systolic, diastolic and mean blood pressure and heart rate were recorded before laryngoscopy and after intubation. 1mg/kg thiopentone was given in all cases before every event of surgery, infiltration of incision with 2% lignocaine and adrenaline 1 in 200,000 was made before incision. Recordings of systolic, diastolic, mean blood pressure and heart rate was done from the arterial tracing, the transducer kept at the level of the external auditory meatus. It was made every 10mts for the first 2hours from the time of dural opening.

At the end of surgery neuromuscular blockade was reversed with glycopyrrolate and neostigmine. Patients were extubated, supplemental oxygen was administered with a mask and for the further care they were sent to intensive care unit.

All the data were entered in SPSS version 18. The mean and standard deviation was calculated for all the parametric variables and for deriving the statistical inference between the two drugs student unpaired T test was used.

Results

The general parameters which were measured among the study subjects of the two groups are shown in table 1. The mean age and the bodyweight of the patients in clonidine and diazepam group were 35.75 years, 54.31 kgs and 38.12 years and 57.75 kgs respectively. The mean duration of anesthesia in clonidine group was 5.06 hrs and for diazepamgroup it was 5.33 hrs. None of these parameters showed any statistical significant difference between the two groups.

The anxiety scoring among the study population was made using the following grading

Score 0 patient quiet and comfortable;
Score 1 patient uneasy;
Score 2 patient worried or anxious;
Score 3 patient very worried or very upset;
Score 4 patient frightened or terrified.

Based on the above mentioned scoring system it was seen that both in the diazepam and clonidine group the anxiety score had come down after the medication and the difference in the score was found to be statistically significant (P<.05). In the clonidine group there were higher number of patients with score 0 when compared to the patients in the diazepam group.

The various hemodynamic parameters measured in the study subjects between the two groups are shown in Table 3. The hemodynamic parameters were initially measured at the baseline (90 mins after taking the oral drug) and later on they were measured at the intervals of 10 mins for 2 hrs. The procedures like intubation, opening of duramater and insertion of and removal of pins were done in that interval. The hemodynamic parameters which were measured are heart rate, systolic and diastolic blood pressure and the mean arterial pressure, the mean and standard deviation of all those

variables are highlighted in Table 3. There was a significant reduction in the heart rate at the end of 90 and 120 mins in the clonidine group when compared to the diazepam group and the other hemodynamic parameters did not show a significant difference between the two groups.

Similarly the blood pressure parameters in both the groups had also shown reduction from base line in the first 60minutes and later on over the period of 2 hours the values had come back to that of the base line values but no statistically significant difference had occurred between the two groups.

The antisialogague effect between clonidine and diazepam group had shown that majority (80%) of the patients in the clonidine group had developed dry tongue 90 minutes after taking clonidine whereas among the patients in the diazepam group only 28% had developed dry tongue, this shows that the antisialogague activity is more with the clonidine than that of the diazepam.

Table 1: Mean age, body weight and the duration of anaesthesia among the study subjects

Parameters	Group I (diazepam)		Group II (Clonidine)		P value
	Mean	SD	Mean	SD	
Age (in years)	38.12	11.16	35.75	10.38	0.597
Body weight (Kgs)	57.75	10.72	54.31	8.58	0.355
Duration of anaesthesia (Hrs)	5.33	1.24	5.06	1.51	0.825

P value derived by applying unpaired T test

Table 2: Anxiety scoring among the study subjects between the two groups before and after premedication

Groups			Anxiety score					P value
		0	1	2	3	4	Mean (SD)	
Group I (diazepam)	Before premedication (N=25)	13	27	9	1	0	1.12 (0.14)	<.001
	After premedication (N=25)	39	11	0	0	0	0.25 (0.10)	
Group II (Clonidine)	Before premedication (N=25)	10	22	15	3	0	1.24 (0.34)	<.001
	After premedication(N=25)	43	7	0	0	0	0.17 (0.09)	

P value derived by applying unpaired T test

Table 3: Hemodynamic parameters among the study subjects between the two groups

Group		Hemodynamic parameters	Minutes						P value
			Baseline	10	20	60	90	120	
Group I	Diazepam	Mean Heart rate (SD)	102 (6.4)	100 (7.5)	94 (5.6)	94 (7.8)	96 (8.2)	94 (8.6)	0.418
		Mean Systolic BP (SD)	138 (7.5)	134 (7.6)	130 (8.6)	130 (9.8)	142 (7.4)	148 (9.4)	0.382
		Mean Diastolic BP (SD)	94 (6.5)	94 (6.8)	92 (7.4)	90 (7.8)	93 (8.5)	97 (9.5)	0.517
		Mean of Mean arterial pressure (SD)	100 (8.6)	97 (7.8)	94 (8.2)	98 (9.4)	100 (9.6)	100 (9.6)	0.815
Group II	Clonidine	Mean Heart rate (SD)	96 (7.9)	94 (8.4)	90 (6.9)	84 (9.2)	80 (8.8)	78 (9.4)	0.014
		Mean Systolic BP (SD)	136 (8.8)	130 (8.6)	128 (7.6)	138 (8.6)	140 (8.9)	142 (9.2)	0.287
		Mean Diastolic BP (SD)	92 (9.2)	88 (8.6)	84 (8.5)	86 (9.2)	96 (9.6)	98 (9.7)	0.428
		Mean of Mean arterial pressure (SD)	98 (8.9)	90 (9.3)	86 (9.7)	90 (8.7)	94 (9.3)	102 (9.6)	0.319
Unpaired T test	P value (inter-group	Mean Heart rate	0.714	0.482	0.318	0.072	<.001	<.001	
		Mean Systolic BP	0.618	0.582	0.718	0.642	0.892	0.739	

	comparison)	Mean Diastolic BP	0.814	0.352	0.285	0.783	0.802	0.938	
		Mean of Mean arterial pressure	0.892	0.652	0.359	0.472	0.538	0.817	

P value derived by applying unpaired T test

Table 4: Antisialogue effect before and after medication between the two groups

Group	Pre-medication		90 minutes Post-medication		P value
	Moist tongue	Dry tongue	Moist tongue	Dry tongue	
Group I (Diazepam) (n=25)	22 (88%)	3 (12%)	18 (72%)	7 (28%)	0.181
Group II (Clonidine) (n=25)	23 (92%)	2 (8%)	5 (20%)	20 (80%)	<.001

P value derived by applying unpaired T test

Discussions

The choice of anaesthetic technique for craniotomy surgeries is mostly limited to general anaesthesia with muscle paralysis, tracheal intubation and intermittent positive pressure ventilation. This study was conducted in 50 adult patients belonging to ASA physical status I and II, to evaluate the effect of clonidine premedication on haemodynamic response in comparison with oral diazepam. Clonidine has an excellent bioavailability after the oral dose and it attains the peak plasma concentrations within 60-90 min[15]. In our study, tablet clonidine was given 90 min before the surgery.

In this study oral clonidine 3.5 mcg/ kg-1 produced both sedation and anxiolysis. The sedation score is almost similar to that of diazepam whereas the anxiety score was less in clonidine group than the diazepam group but was not found to be statistically significant and a similar type of results was also observed by the study done by Dipak L Raval etal[16], Rudra A etal[17] and Das A K etal[18]. The sedative effect of clonidine is because of the reduced tonic activity of locus coeruleus[19]. Sedation and anxiolysis caused by clonidine are elicited through central alpha-2 adrenergic receptors and it is being considered as an anaesthetic adjuvant.

The heart rate in the clonidine group was found to be reduced over a period of time during craniotomy when compared to the diazepam group and the difference was found to be statistically significant. The decrease in the pulse rate after clonidine is due to the reduction of the sympathetic outflow, the simultaneous increase of parasympathetic tone of central origin and the influence of clonidine on neurons which receive baroreceptor afferents[20].

There was a fall in systolic, diastolic and mean arterial pressure in both clonidine and diazepam group but the difference was not found to be statistically significant. Clonidine being an alpha – 2 adrenoceptor agonist interacts with the catecholaminergic neuronal system which modulates tonic and phasic (reflex) blood pressure control and reduces the release of norepinephrine from nerve endings both centrally and peripherally and causes reduction in arterial pressure[21].

Sympatho-adrenal activation due to laryngoscopy and endotracheal intubation causes rise in arterial blood pressure and tachycardia. But this can be reduced with administering low doses of oral clonidine as suggested by Carabine et al in his study. Prevention of tachycardia in response to laryngoscopy and intubation and the slowing of the heart rate induced by clonidine share a complex underlying mechanism[22].

There is little physiological basis for alpha-2 adrenergic receptor stimulation induced respiratory depression. In our study also we did not experience any case of respiratory depression as their respiratory rate and the oxygen saturation were normal[23].

In the present study clonidine premedication had caused a substantial degree of dryness of mouth (antisialogague effect), which might be due to the effect on presynaptic alpha adrenoceptors in the brain stem as well as on parasympathetic nerves which supplies the salivary glands[24].

Conclusion

Clonidine being used as a premedication has almost the same effect on sedation and a better anxiolytic property than that of diazepam. Clonidine had shown a better response in controlling tachycardia than diazepam. The additional effect on causing dryness of mouth due its antisialogogue activity in clonidine group makes it more comfortable for anaesthetist in considering clonidine better than diazepam in premedication to be used for craniotomy.

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